REMARKS

Reconsideration of the application in light of the following remarks is respectfully requested.

I. Status of the Claims

Claims 37 and 52-54 have been amended as discussed in detail below, and new claims 66 to 72 have been added. These amendments are fully supported by the specification also discussed below. No new matter has been added by these amendments. Therefore, claims 37, 42-44, 48, 52-54, 56-57 and 66-72 are presently pending and at issue in the application.

Claim 37 has been amended to remove reference to "mouth." The amendment removes a claim element that is not essential to the claimed invention and therefore does not introduce new matter to the specification. *See* MPEP §2163.

Claim 37 has also been amended to further clarify that the bystander antigen is present in an organ or tissue afflicted by immune attack during said disease. Support for this amendment is found throughout the specification, for example, at page 11, lines 25 to 27, and in original claim 27. This amendment does not introduce new matter to the specification.

Claims 52-54 have been amended to properly depend from independent claim 48. The amendment corrects an obvious typographical error and does not introduce new matter to the specification.

New claims 66-72 have been added. Claim 66, which depends from claim 37, introduces the limitation that the bystander be administered by inhalation. Support for new claim 66 is found in the specification at page 23, lines 25-31 and in original claim 7. Claims 67 and 68, which depend from claim 37, introduce the limitation that the bystander is glucagon or glutamic acid decarboxylase, respectively. Support for new claim 67 is found in the specification at page 19, lines 15-23. Support for claim 68 is found at page 19, Table 1. Claims 69 through 72, which depend from claims 37 and 48 respectively, introduce the limitation that the bystander antigens of the respective methods and pharmaceutical compositions are pure or purified. Support for new claims 69 through 72 is found in the

specification at page 15, lines 20 to 24, and at page 29, lines 16 to 21. No new matter has been introduced to the specification by these amendments.

II. Claim Rejections

A. Rejections under 35 U.S.C. §112, first paragraph

1. *Rejections for inadequate written description*

Presently, claim 37 and dependent claims 42-44 have been rejected for failure to satisfy the written description requirement. The Examiner states that the claim limitation, whereby the bystander antigen is administered to the mouth, is not supported by the specification. Without conceding the correctness of the Examiner's rejection, claim 37 has been amended to omit reference to administration by mouth. Amended claim 37 currently recites a method of treating an autoimmune disease in a host by administering a bystander antigen by nose to the host. Applicants submit that the present amendment addresses and overcomes the instant rejection and therefore respectfully request that the Examiner withdraw the rejection.

2. *Rejections for lack of enablement*

Claims 37, 42-44, 48, 52-54 and 56 are rejected under 35 U.S.C. §112, first paragraph, for lack of enablement. Particularly, the Examiner states that the teachings of the specification and in particular, the teachings regarding the suppression of an immune response by oral administration of a bystander antigen, may not be extrapolated to suppression of an autoimmune disease by nasal administration of a bystander antigen. Therefore, the specification does not enable claims directed to administration of a bystander antigen by inhalation. The Examiner's rejection is premised on the following conclusions:

(1) The art at the time of the invention was highly contradictory for oral tolerance, and remains so today. Therefore, one of ordinary skill could not have readily practiced the claimed invention at the time of filing.

(2) There is a lack of correlation between active suppression of an autoimmune disease in an animal model and successful suppression in humans.

(3) The specification is devoid of any example demonstrating suppression of an autoimmune disease, in either a human or animal, by administering a bystander antigen by inhalation.

The Examiner has cited WO 02/053092 to Harats et al. ("Harats") for the proposition that oral tolerization is highly unpredictable. *See* Office Action Mailed June 9, 2004, page 5. Applicants submit that the Examiner has ignored several pertinent teachings of Harats and therefore has mischaracterized the teachings of the art. For example, the Examiner has ignored Harats' citation of the applicants' own successful induction of tolerance by oral and nasal administration of bystander antigens. Citing the teachings of Wiener, Harats states, "These treatments induce tolerance, orally or mucosally, e.g., by inhalation, using as tolerizers autoanitigens or bystander antigens." (Harats, page 12, lines 5-12, citing U.S. Patent No. 5,935,577 to Weiner, et al.). Harats also teaches that in some instances nasal administration of antigens is more successful at inducing tolerance than oral administration, concluding,

> Therefore, immunogenic compounds intended for mucosal as well as intravenous or intraperitoneal administration should be adaptable to nasal and other membranous routes of administration.

(Page 15, lines 1-10, emphasis added). Provided with the teachings of Harats alone, which the Examiner has cited as demonstrative of the state of the art, one of ordinary skill in the art would readily appreciate that the teachings of the instant application regarding oral administration could be extrapolated to nasal administration of a bystander antigen.

The teachings of the present specification are consistent with the teachings of Harats. U.S. Patent Application Serial No. 454,806, incorporated by reference at page 24, lines 3-4 of the present specification, teaches the induction of tolerance by inhalation of myelin basic protein (MBP) and the suppression of experimental allergic encephalomyelitis (EAE)[1]. The matter incorporated by reference is considered part of the application and must be given full

[1] A number of U.S. Patents based upon U.S. Application Serial No. 456,806, have issued. For example U.S. Patent No. 5,645,820, which is a continuation of Application Serial No. 053,306; which is a continuation of the '806 application.

consideration. *See* MPEP §2163.07(b). The '806 application also discloses the suppression of adjuvant arthritis following administration of collagen via inhalation. (Example, 4, column 14, lines 4-9). Additionally, the '806 application teaches that nasal administration of antigens is more effective in preventing and treating autoimmune diseases in mammals than administration of the same autoantigens in solid form via the oral route. (Column 4, lines 16-24, and Figure 1).

Both Harats teachings and the applicants' own discovery that nasal administration is more effective at inducing tolerance and suppressing an autoimmune disease compared to oral administration support a finding of enablement of the present claims. Additional support for this finding is found in the instant specification itself. The specification teaches that the mechanism of bystander suppression is the same, regardless of the route of antigen administration. (Page 12, lines 3-10). For example, both oral and inhalation administration of a bystander antigen result in entry of the antigen into the small intestine where it is delivered to the Peyer's Patches. Delivery of the antigen to the Peyer's Patches then results in induction of $CD8^+$ T-cells, which results in the active suppression of an autoimmune response. The induction of $CD8^+$ T-cells is neither dependent on the route of administration or the antigen administered. (Page 12, lines 3-10). Both oral and nasal administration deliver the antigen to the Peyer's Patches where they initiate a tolerizing reaction. The specification includes working examples of oral tolerization and provides detailed guidance for delivery of an antigen to the Peyers Patches by inhalation (*see, e.g.*, page 23, line 25 to page 24, line 12). Accordingly, one of ordinary skill in the art would have been able to practice the full scope of the claimed invention without undue experimentation. Thus, the specification teaches that tolerance could be induced by inhalation of a bystander antigen and that tolerance is not dependent upon either the route of administration or the antigen being administered.

The applicants have successfully demonstrated suppression of a number of autoimmune diseases using a number of bystander antigens in several different well established and widely accepted animal models. *See generally*, Examples 5 and 6. The animal models employed by the applicants have been specifically designed to investigate autoimmune diseases in the scientific field. Experimental allergic encephalomyelitis (EAE) is the animal model for multiple sclerosis (MS), and adjuvant arthritis (AA) is the well

established animal model for rheumatoid arthritis (RA). The correlation between these animal models and human disease is set forth in the specification itself. (Page 14, line 32 to page 15, line 11). Moreover, each of these animal models are widely accepted in the art as models for human autoimmune diseases and it has been clearly established that the results obtained with an animal model disease are applicable to the corresponding the human disease. *See, e.g.*, Van Eden et al., (1985) *Proc. Natl Acad. Sci.*, 82:5117-5120 (Exhibit A). Therefore, the skilled artisan would expect that experimental results obtained for the animal models in the present application could be extrapolated to a human model for suppression of the corresponding human disease.

The Examiner's reference to the applicants' clinical trials as evidence of lack of enablement is misplaced. The inability of an invention to yield a commercially successful embodiment is not pertinent to the determination of enablement. Furthermore, reliance on post filing clinical trials is counter to established precedent that mandates assessment of enablement as of the filing date, not in light of later developments. *See CFMT, Inc. v. Yieldup Intn'l Corp.*, 349 F.3d 1333 (Fed. Cir. 2003) (Federal Circuit holding that the district court erred in relying upon post filing evidence when determining enablement, stating "Enablement does not require an inventor to meet lofty standards for success in the commercial marketplace."). As noted above, at the time the application was filed it was accepted in the art that the animal models utilized therein were predictive of success in humans. *See* Van Eden et al. at page 5117 (Exhibit A). The fact that post filing clinical trials, that did not even measure the suppression of an autoimmune disease as presently claimed, did not satisfy FDA criteria for efficacy, is irrelevant.

Finally, the fact that the specification does not disclose experimental evidence of inducing tolerance by inhalation of a bystander antigen is not itself sufficient to warrant a rejection for lack of enablement. It is well established that applicants are not required to provide working examples of all embodiments of the claimed invention. *In re Long*, 368 F.2d 892 (CCPA 1966) (court holding that the absence of a working example does not in and of itself compel the conclusion that a specification does not satisfy the requirements of § 112). Rather, applicants must provide a disclosure that would guide the skilled artisan to practice the full scope of the claimed invention without undue experimentation. *In re Wands*, 858

F.2d 731 (Fed. Cir. 1988). The applicants have done just that. As noted above, the present specification incorporates by reference the '806 application, which provides experimental evidence of inducing tolerance by nasal administration of autoantigens. In view of the teachings of the '806 application and those of the present specification regarding the induction of tolerance by nasal administration of bystander antigens and the subsequent suppression of an autoimmune disease (*see, e.g.,* page 11, line 1 through page 12, line 21), the skilled artisan could readily induce tolerance by administration of a bystander antigen and suppress an autoimmune disease without undue experimentation. This conclusion is supported by the declaration of Dr. Von Herrath (of record)[2].

The Examiner has previously stated that the declaration of Dr. Von Herrath is "...devoid of extrinsic probative evidence that establishes the claimed method is effective in suppression of autoimmune disease..." and contradictory of the teaching of Harats. *See* Office Action Mailed June 9, 2004, page 9. However, as noted above, Harats, like Dr. Von Herrath, teaches that antigens suitable for muscosal delivery would be expected to be suitable for administration by inhalation. Therefore, Harats supports, rather then contradicts the declaration of Dr. Von Herrath. Moreover, Dr. Von Herrath, does provide probative extrinsic evidence in support of his conclusion that one of ordinary skill could practice the claimed invention without undue experimentation.

In his declaration, Dr. Von Herrath stated that the teachings of suppression of an autoimmune disease by administration of an antigen are pertinent to suppression of an autoimmune disease by administration of a bystander antigen. (Von Herrath, page 10, para. 15). Both utilize the mechanism of active suppression wherein an antigen is administered mucosally in order to regulate an immune response. (Von Herrath, page 10, para. 15). The present invention is premised on the same mechanism that effectively suppressed an autoimmune disease following nasal administration of an autoantigen, and therefore, Dr. Von Herrath concluded, "... it became likely that these conclusions could be extended to bystander antigens." (Von Herrath, page 11, para. 15).

[2] Dr. Von Harreth Declaration ("Von Harreth"), submitted November 1, 2000, with Supplemental Response, Paper No. 25. Dr. Von Harreth is the author of over 30 publications on the subject of immunology of the autoimmune diseases, including several articles relating to bystander suppression.

Therefore, in view of the foregoing remarks, applicants respectfully request that the rejection of claims 37, 42-44, 48, 52-54 and 56, under 35 U.S.C. §112, first paragraph, be withdrawn.

B. Rejections under 35 U.S.C. §112, second paragraph

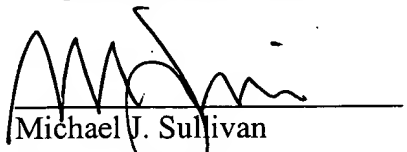
Claim 37 has been rejected as indefinite. Without conceding the correctness of the Examiner's rejection, claim 37 has been amended to further clarify that the bystander antigen is present in an organ or tissue afflicted by immune attack during said disease. Support for this amendment is found, for example, at page 11, lines 25 to 27 of the specification, and in original claim 27. It is believed that the amendment addresses and overcomes the present rejection and therefore applicants respectfully request that the rejection be withdrawn.

CONCLUSION

In view of the foregoing it is believed that the presently pending claims are in condition for allowance, and it is respectfully requested that the application be reconsidered and that all pending claims be allowed and the case passed to issue. If there are any other issues remaining which the Examiner believes could be resolved through a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the telephone number indicated below.

Respectfully submitted

Dated: December 9, 2004



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Immunology

Arthritis induced by a T-lymphocyte clone that responds to *Mycobacterium tuberculosis* and to cartilage proteoglycans

(autoimmunity/cross-reactivity/adjuvant arthritis)

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ABSTRACT **Adjuvant arthritis characterized by chronic inflammation of the joints of rats is induced by immunization to *Mycobacterium tuberculosis*. To learn how autoimmune arthritis may be caused by a microbial antigen, we isolated a T-lymphocyte clone specific for *M. tuberculosis* antigens that was strongly arthritogenic. We now report that the clone recognized, in addition to *M. tuberculosis* antigens, antigens present in human synovial fluid, medium of chondrocyte cultures, and proteoglycans purified from cartilage. These observations indicate that the target antigen for the arthritogenic clone resides in the proteoglycan component of cartilage. As this arthritogenic clone shows specificity for both a *M. tuberculosis* antigen and a cartilage constituent we conclude that disease is probably caused by antigenic cross-reactivity. Thus, an autoimmune disease may be triggered by structural mimicry between antigens in the environment and self-antigens in the individual.**

Adjuvant arthritis can be produced in genetically susceptible rats by inoculation of *Mycobacterium tuberculosis* emulsified in oil (complete Freund's adjuvant) (1). The disease has been thought to involve an autoimmune process because it can be transferred by lymphocytes from affected to healthy rats (2). Adjuvant arthritis therefore poses the question of how an autoimmune disease is triggered by immunization to microbial antigens. Our strategy for investigating autoimmunity has been to isolate and grow as long-term cell lines specifically autoimmune T lymphocytes from animals with experimentally induced diseases such as experimental autoimmune encephalomyelitis (3) or experimental autoimmune thyroiditis (4). These cell lines are functional and can mediate the specific disease *in vivo* or under suitable conditions can be used as vaccines to endow recipient animals with resistance to active induction of the particular disease (4–6).

The development of functional T-lymphocyte lines in the experimental autoimmune encephalomyelitis and experimental autoimmune thyroiditis models was guided by knowledge of the target self-antigens, myelin basic protein and thyroglobulin, that can be used to select the lymphocytes *in vitro*. In adjuvant arthritis, in contrast, the putative target self-antigen was unknown. Nevertheless, an arthritogenic line, designated A2, was raised from lymph nodes of affected rats using ground *M. tuberculosis* as the selecting antigens (7). We reasoned that line A2 was arthritogenic because some of its cells had receptors specific for *M. tuberculosis* antigens that possibly mimicked self-antigens in the joints.

Subsequent cloning of the A2 T-cell line provided us with a T-lymphocyte clone that was both immune to *M. tuberculosis* and also arthritogenic (8). This clone, A2b, was exploited in the present investigation as a probe to detect the presumed target self-antigen by measuring the *in vitro* proliferative responses of the clone and also its *in vivo* delayed type hypersensitivity reactivity to various joint substances.

METHODS

Rats. Inbred Lewis rats, 2–4 months old, were obtained from the Animal Breeding Center of this Institute. Rats were matched for age and sex in each experiment.

Clone A2b. The isolation, cloning, and maintenance of the T-lymphocyte clone A2b has been described previously (8). Briefly, a line reactive to *M. tuberculosis* was first isolated from draining lymph nodes of Lewis rats immunized with complete Freund's adjuvant (7). The established line was cloned by seeding a dilution of 0.1 cell per well (96-well tissue culture plate, Costar, Cambridge, MA) in the presence of irradiated (1500 rads; 1 rad = 0.01 gray) syngeneic thymocytes (2×10^7/ml) and *M. tuberculosis* (10 μg/ml). Cloned cells were expanded in interleukin 2-containing propagation medium. Every 2–4 weeks clone A2b was restimulated by incubation with *M. tuberculosis* and accessory cells for 3 days and then transferred back into propagation medium as described (8).

Response to Antigens. The cloned cells were incubated in flat-bottomed microtiter plates in triplicate wells (3, 7, 8). Each well contained 2×10^4 cloned cells and 2×10^6 1500-rad–irradiated syngeneic thymocytes in 0.2 ml of proliferation medium (Dulbecco's modified Eagle's medium supplemented with 1% syngeneic rat serum) with antigens in various concentrations. After 24 hr of incubation, 1 μCi (1 Ci = 37 GBq) of [^{3}H]thymidine (specific activity, 10 Ci/mmol; Nuclear Research, Negev, Israel) was added to each well and incubation was continued for 18 hr. Cultures were harvested on fiberglass filters and thymidine incorporation was measured using a liquid scintillation counter. Thymidine incorporation is expressed as mean cpm of test cultures minus mean cpm of control cultures without antigen ± standard deviation (Δcpm).

Antigens. The following antigens were used: heat-killed *M. tuberculosis* $H_{37}Ra$ purchased from Difco; proteoglycan extracted as described by Haskall and Kimura (9) from rat and pig cartilage by G. Hunter (kindly donated by A. Czitrom, Mount Sinai Hospital, Toronto); conditioned medium of chicken chondrocyte culture harvested from a 12-day-old suspension culture of chondrocytes (5×10^5 cells per ml) in soft agar (10); cell-free synovial fluid obtained by puncture from a human osteoarthritic joint; collagen type II derived from rat cartilage and keratan sulfate derived from human cornea (kindly donated by E. J. Miller of the Alabama Medical Center, Birmingham, and T. Laurent of the Univer-

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sity of Uppsala, respectively); chondroitin sulfate (purity grade III) and hyaluronic acid (purity grade IV) purchased from Sigma; and core protein of cartilage proteoglycan prepared as described (11).

Delayed Type Hypersensitivity. Delayed type hypersensitivity induced by clone A2b was measured as follows. Clone A2b was activated by restimulation in proliferation medium in the presence of 10 μg of *M. tuberculosis* antigen/ml and irradiated syngeneic thymocytes as accessory cells (3, 7, 8). Cells (2×10^7) were injected intravenously into groups of five irradiated (750 R) or intact Lewis rats. To test for delayed type hypersensitivity, 5 days later 0.1 ml of each antigen solution was injected with a 27-gauge needle into the pinna of a rat's ear at a concentration of 200 μg/ml for *M. tuberculosis* and chondroitin sulfate and at a dilution of 1:20 for synovial fluid. Ear thickness was measured with a micrometer caliper (Ames, Waltham, MA) at 24 hr and at 48 hr after injection of the antigen. No significant differences were observed between measurements at 24 and 48 hr and the results are shown at 24 hr. The results are expressed as mean percent increase of ear thickness (mean ear thickness 24 hr after injection − mean ear thickness before injection) ± SD. Delayed type hypersensitivity reactions were similarly measured in rats in which active adjuvant arthritis had been induced as described (7, 8) 4 weeks earlier.

RESULTS

As shown in Fig. 1, the cells of clone A2b responded *in vitro* ([^{3}H]thymidine incorporation) to synovial fluids isolated from humans suffering from osteoarthritis, to conditioned medium of chicken chondrocytes grown in suspension culture, and to preparations of rat or porcine proteoglycans. Similar results were obtained using synovial fluids from patients with rheumatoid arthritis (data not shown). These responses were considerable, although the [^{3}H]thymidine incorporation of clone A2b stimulated by *M. tuberculosis* exceeded them by an order of magnitude. Responses to collagen type II, the predominant collagen constituent of cartilage, and to the glycosaminoglycan constituents of cartilage, hyaluronic acid and keratan sulfate, were invariably found to be negative. The lack of responsiveness to collagen type II clearly distinguishes this model from collagen II arthritis (12). The positive responses of clone A2b to proteoglycan-containing preparations such as synovial fluid and chondrocyte medium and to purified proteoglycans were specific for that clone and were not due to contamination of the antigens with some nonspecific mitogen. No response to these preparations was shown by two other clones, a non-arthritogenic but *M. tuberculosis*-specific clone that had been isolated from the same line as had clone A2b and an encephalitogenic, basic protein specific T-lymphocyte clone (results not shown).

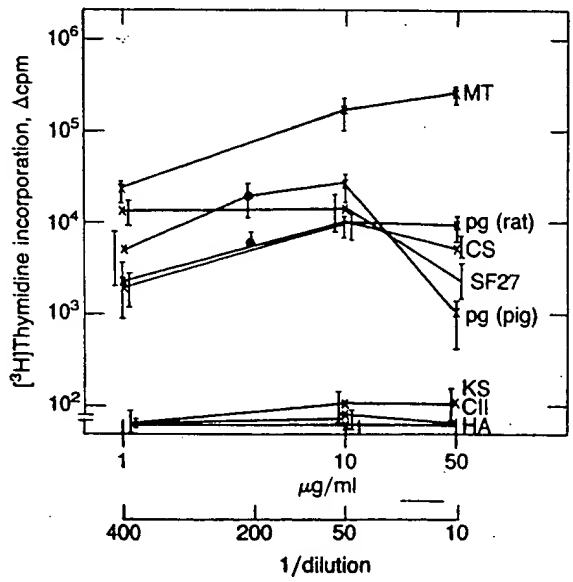

FIG. 1. *In vitro* [^{3}H]thymidine incorporation by the arthritogenic T-lymphocyte clone A2b after stimulation by *M. tuberculosis* (MT) and various cartilage components. pg, Proteoglycan preparation of rat or pig cartilage; CS, conditioned medium of chicken chondrocyte culture; SF27, cell-free synovial fluid from a human osteoarthritic knee.

It has been difficult to identify the particular epitope which the cells of clone A2b recognized in synovial fluid and proteoglycan preparations. For example, the cells of clone A2b showed [^{3}H]thymidine incorporation in two of four experiments when incubated *in vitro* with a preparation containing chondroitin sulfate (results not shown). The lack of uniformity in the response to chondroitin sulfate might be explained by the observation that carbohydrate antigens often are not taken up and processed efficiently by antigen-presenting cells *in vitro* (13).

We observed previously that T-cell lines transferred antigen-specific delayed type hypersensitivity skin reactions and that irradiation of the recipient rats enhanced the magnitude of transferred reactivity (14). Clone A2b which bears the W3/25 marker of helper/delayed hypersensitivity T lymphocytes (8) was tested for its ability to transfer delayed type hypersensitivity to *M. tuberculosis* or to the cross-reactive determinant present in joint materials. Fig. 2 shows the results of delayed type hypersensitivity reactivities as measured by ear swelling 24 hr after intrapinnal injection of antigen into rats, some of which had been irradiated and/or had received clone A2b. It can be seen that in irradiated recipients clone A2b transferred delayed type hypersensitivity reactivity not only to *M. tuberculosis* but also to antigens present in synovial fluid and to a chondroitin sulfate preparation of proteoglycan. A delayed hypersensitivity response was also elicited by a core protein of proteoglycan prepared by exhaustive digestion of the Swarm rat chondrosarcoma proteoglycan by hyaluronidase (11) (results not shown). Histologic examination of the ear swelling confirmed that this response was caused by a delayed type hypersensitivity reaction.

A delayed type hypersensitivity reaction was elicited in the nonirradiated recipients of clone A2b by *M. tuberculosis* but not by chondroitin sulfate or synovial fluid, an observation for which there is no obvious explanation. It is conceivable that radio-sensitive regulatory mechanisms control responsiveness to proteoglycan self-determinants, a hypothesis supported by the finding that irradiation of the recipient is a prerequisite for induction of arthritis by line A2 or clone A2b (7, 8). However, irradiation of the recipient was not required for other line-mediated autoimmune diseases such as experimental autoimmune encephalitis in rats (3) or experimental autoimmune thyroiditis in mice (4).

Reactivity to proteoglycans was also observed in intact rats suffering from active adjuvant arthritis. Table 1 shows the delayed type hypersensitivity reactivities of rats that had been inoculated with complete Freund's adjuvant 4 weeks earlier to induce arthritis. Similar to the irradiated recipients of clone A2b, these unirradiated rats responded to *M. tuberculosis* and in addition to synovial fluid and to the chondroitin sulfate and core protein components of proteoglycan. They did not respond to the keratan sulfate chains of proteoglycan. Thus, the proteoglycan cross-reactivities demonstrated by the arthritogenic clone A2b were confirmed in unirradiated rats with actively induced disease.

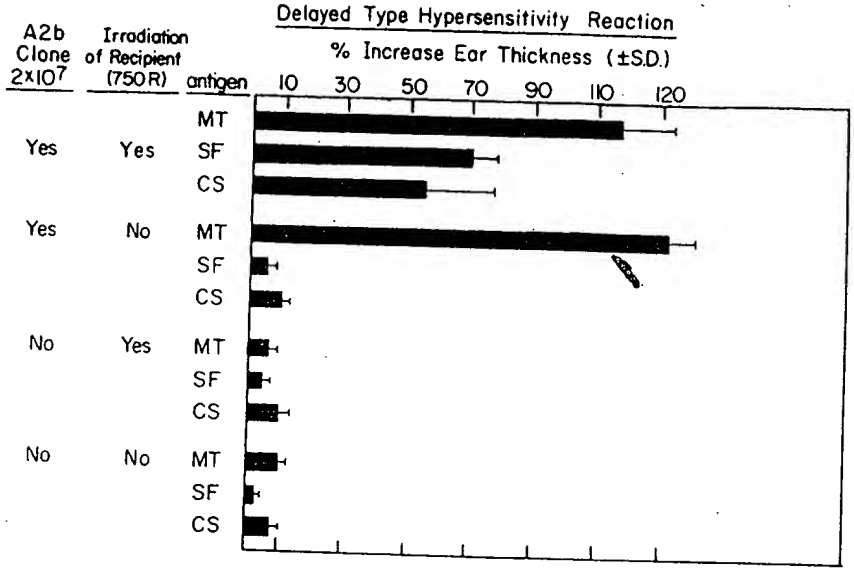

FIG. 2. Delayed hypersensitivity ear test. The % increase in ear thickness was measured 24 hr after injection of antigens; MT, *M. tuberculosis*; SF, human synovial fluid; CS, chondroitin sulfate.

DISCUSSION

The results of this study demonstrate that a T-cell clone selected by the strength of its reactivity to mycobacterial antigens also recognized part(s) of a proteoglycan molecule of cartilage, possibly the core protein or the chondroitin sulfate chain. A more precise identification of the epitope thus far has been hampered by the paucity of techniques suitable for isolation of undenatured fragments of proteoglycans. In general, responses to core protein have tended to be stronger than those observed to chondroitin sulfate and it is possible that the responses to chondroitin sulfate preparations may have been due to contamination with core protein.

As a monoclonal population of lymphocytes should deploy antigen receptors of a uniform shape, the sensitivity of the cells of clone A2b to both *M. tuberculosis* and proteoglycans argues for the existence of structural mimicry between their parts. The differences in magnitude of [^{3}H]thymidine incorporation of clone A2b in response to *M. tuberculosis* and to proteoglycan materials suggests that their mimicry may be imperfect or that the self-epitope might be only a minor component of the proteoglycan preparations that were available to us.

Cross-reactivity between microbial antigens and self-molecules has been seen previously by means of serology. Group A streptococci were shown to cross-react with human myocardium, a mimicry that might play a role in the pathogenesis of rheumatic fever (15). Monoclonal antibodies to DNA raised from the lymphocytes of patients with lupus erythematosus bind cardiolipin and other substances and it has been proposed that DNA-binding antibodies in these patients may have arisen in response to cross-reactive antigens introduced by bacteria (16). Worthy of note is the association of some types of arthritis with previous infection of humans of *HLA-B27* genotype with enteric bacteria (17).

The demonstration of a serological cross-reactivity, although intriguing, does not prove its role in pathogenesis. We have now shown in the present investigation that the arthritogenic clone A2b itself is the very agent that defines a structural mimicry between *M. tuberculosis* and joint cartilage. Hence, this cross-recognition indeed may incite the immune attack on the joints characteristic of adjuvant arthritis. Moreover, the pathogenic consequences of antigenic mimicry between mycobacteria and joint cartilage may not be limited to rats; a significant number of persons treated for cancer by repeated immunization with the Bacillus Calmette–Guerin strain of mycobacteria have developed arthritis (18).

Table 1. Delayed type hypersensitivity response of rats with active adjuvant arthritis

Antigen	% increase in ear thickness
M. tuberculosis	86 ± 7
Synovial fluid	33 ± 14
Core protein	48 ± 20
Chondroitin sulfate	16 ± 8
Keratan sulfate	0 ± 2

Groups of five Lewis rats were inoculated with complete Freund's adjuvant to induce active adjuvant arthritis (7, 8). Four weeks later delayed hypersensitivity responses were assayed. The background swelling induced by the antigens in normal rats was subtracted from the mean response. Results represent mean ± SD.

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